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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/589,255	06/07/2000	Charles J. Link JR.	P04091US1	8671

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MCKEE, VOORHEES & SEASE, P.L.C.
801 GRAND AVENUE
SUITE 3200
DES MOINES, IA 50309-2721

EXAMINER	
BECKERLEG, ANNE M	

ART UNIT	PAPER NUMBER
1632	7

DATE MAILED: 06/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/589,255	Applicant(s) LINK ET AL.	
	Examin r Anne Marie Becherleg	Art Unit 1632	

-- Th MAILING DATE of this communication app ars on th cover she t with th correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

Applicant's amendment and sequence listings in paper and in CRF received on 4/9/02 have been entered. This application is now in compliance with 37 CFR 1.821-1.825. Claims 1-18 are pending in the instant application. An action on the merits follows.

Those sections of Title 35, US code not included in this action can be found in the previous office action.

Double Patenting

The rejection of claims 1-4, 6-12, and 15 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4-7 of U.S. Patent No. 5,869,035, hereafter referred to as the '035 patent, is maintained. Applicant's arguments have been fully considered but have been found unpersuasive in overcoming the instant rejection for reasons of record as discussed in detail below.

The applicant states that a terminal disclaimer over U.S. Patent No. 5,869,035 has been submitted to the office. However, a terminal disclaimer was not received with the instant response. If applicants have in fact submitted such as document, the office requests that a copy be provided for entry into the instant record. In view of the fact that a terminal disclaimer is not of

record in the instant case, applicant's argument that the submission of a terminal disclaimer overcomes the instant grounds of rejection is moot.

The applicant has also traversed the instant rejections. The applicant argues that claim 5 of the '035 patent recites that the vector producer cell line does not contain an active murine alpha (1,3) galactosyl transferase gene, where in the applicant's invention the surface glycosylation of the cells is alpha (1,3,) galactosyl epitopes. Please note that while claim 5 of the '035 patent does state that the vector producer cell line does not contain an active murine alpha (1,3) galactosyl transferase gene, claims 4 and 6 state that the vector producer cell line comprises a recombinant mini-viral HSV plasmid vector which encodes a transcription unit sequence encoding an alpha (1,3) galactosyl transferase gene. Thus, the vector producer cell line of claim 6 of the '035 patent, which depends on claim 4, clearly has surface glycosylation which contains alpha (1,3) galactosyl epitopes resulting from the expression of the alpha (1,3) galactosyl transferase gene contained in the HSV plasmid vector. Furthermore, it is noted that applicant's claims 1-2, 6-11, and 15 do not recite the limitation that the xenogeneic cells have alpha (1,3) galactosyl epitopes. The applicant further argues that the instant invention is distinct from that of the '035 patent in that the instant invention provides methods for inducing an immune reaction to attack tumor cells. This argument is not compelling as complement killing of a tumor, as specifically recited by the '035 claims, is an immune reaction. Further, the applicant's arguments that case law does not support inherency for process claims are refuted by *Ex parte Novitski*, wherein claims directed to a method for protecting a plant from plant pathogenic nematodes by inoculating the plant with a nematode

inhibiting strain of *P. cepacia* was rejected over a U.S. Patent which disclosed the inoculation of *P. cepacia* for protecting plants from fungal disease and was silent in regards to nematode inhibition. The board found that nematode inhibition was an inherent property of the bacteria. In the instant case, the generation of immune responses leading to hyperacute rejection of a tumor is an inherent property of the xenogeneic retroviral producer cells recited by the '035 patent. Thus, the rejection of record stands.

The rejection of claims 1-4, 6-12, and 15 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,869,035, hereafter referred to as the '035 patent, is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

As noted above, the terminal disclaimer referred to by the applicant's has not been received by the office. As such, it cannot be relied upon to overcome the instant grounds of rejection. Applicant's specific arguments regarding the teachings of the '035 patent have been addressed in detail above.

Claim Rejections - 35 USC § 112

The rejection of claims 1-16 and 18 under 35 U.S.C. 112, first paragraph, for scope of enablement is maintained. Applicant's arguments have been fully considered but have not been

found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that the specification meets the standards for enablement set forth in *Ex Parte Forman* . The applicant further argues that based on the evidence of record, the office has not provided sufficient evidence to demonstrate non-enablement, citing *In re Brana, In re Marzochhi*, and *In re Wands*. In response, it is noted that 35 U.S.C. 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). Furthermore, the previous office action analyzed the specification in direct accordance to the factors outlined in In re Wands, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by publications from the prior art for the finding of a lack of enablement for the instant methods. In addition, case law including the Marzocchi decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see *In re Marzocchi* 169 USPQ 367, and *Ex parte Sudilovsky* 21 USPQ2d 1702). Further, the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). Ultimately, case law states that ".. the disclosure of an application shall inform those skilled in the

art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970.

The previous office action indicated that the specification, while being enabling for methods of inhibiting the growth of a solid tumor comprising the direct administration to a solid tumor of a xenogeneic retroviral producer cell line which comprises a retrovirus encoding HSV-TK alone or in combination with (1,3) galactosyltransferase, followed by the administration of gancyclovir, does not reasonably provide enablement for methods of treating tumors or methods of treating tumor comprising inducing hyperacute rejection wherein the method steps comprise the injection or infusion of any and all xenogeneic cells. The applicant claims as written are broad and read on numerous embodiments of the invention which the specification does not enable. In particular, the previous office action stated that the specification does not provide an enabling disclosure for the induction of treatment of tumors by inducing hyperacute rejection through any means or by the injection/infusion of any type of xenogeneic cells to any type of host mammal.

Specifically, the previous office noted that the specification is directed to the generation of hyperacute immune responses in humans against alpha (1,3) galactosyl epitopes that are present on non-old world primates. The specification does not disclose any other protein, glycoprotein or carbohydrate which causes hyperacute rejection of cells expressing the protein, glycoprotein or carbohydrate in vivo in humans or in any other mammals. Further, as alpha (1,3) galactosyl epitopes are expressed in the majority of mammals, the disclosed methods of inducing hyperacute

immune responses to alpha (1,3) galactosyl are therefore limited to the introduction of non-old world primate cells to old world primates such as humans. Applicant's claims are not so limited, and the applicant has provided no arguments regarding this grounds of rejection.

It was also noted that the specification fails to disclose any means for inducing hyperacute rejection other than the introduction of murine vector producer cell lines which express a retrovirus encoding a gene such as HSV-TK or alpha (1,3)galactosyl transferase to humans. The specification, while demonstrating that murine retroviral producer cells expressing HSV-TK are killed by hyperacute rejection in vivo in patients and that humans cells transduced with alpha (1,3) galactosyltransferase are lysed by human serum in vitro, fails to provide sufficient guidance as to the level of expression of alpha (1,3) galactosyl epitopes or the level of complement activation required to induce hyperacute immune responses in vivo and further to produce a therapeutic immune or innocent bystander effect on local tumor cells. Although the specification and the art at the time of filing disclose that the introduction of xenogeneic cells such as murine or porcine cells to humans results in their rapid destruction by complement fixation or preformed anti-xenogeneic antibodies, neither the art nor the specification provides any evidence that the destruction of the any xenogeneic cell or xenogeneic viral producer cell in vivo results in any observed tumor treatment in the absence of tk/ganciclovir therapy. Thus, from the teachings in the art and the data provided in applicant's specification, it would appear that hyperacute immune responses to a xenogeneic cell alone are not sufficient to induce significant killing of tumor cells. The applicant has not addressed these issues.

Furthermore, the previous office stated that the specification fails to provide guidance for the expression of any genes other than HSV-TK and alpha (1,3) galactosyltransferase in the xenogeneic cells of the instant invention or teach that the expression of any other gene in a xenogeneic cell results in immune mediated bystander killing of tumors; and that at the time of filing, the art taught that the immunotherapy of tumors using cell based and/or gene based therapies was considered highly unpredictable (Ross et al., Verma et al., and Orkin et al.). The applicant's argue that while these references teach the "difficulties" associated with gene therapy, this does not prove that the claimed invention is not enabled at the time of filing. The office does not have to "prove" that the claims as written are not enabled by the specification. 35 U.S.C. 112, first paragraph, simply requires that office provide reasons "..to doubt the objective truth of the statements contained in the specification"(In re Marzocchi). As noted above, case law including the Marzocchi decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see In re Marzocchi 169 USPQ 367, and Ex parte Sudilovsky 21 USPQ2d 1702). Ross et al., Verma et al., and Orkin et al. were cited to establish the state of the art of gene therapy and immunotherapy of cancer at the time of filing. The combined teachings of these references clearly demonstrate that skilled artisan considered gene therapy of cancer as unpredictable.

Thus, having properly analyzed the specification in accordance to the factors identified in In re Wands, the office has concluded that in view of the art recognized unpredictability of inducing therapeutically effective anti-tumor immune responses in vivo, the lack of guidance

provided by the specification for means of inducing a hyperacute response in any mammal other than the administration of viral producer cells which express HSV-TK or alpha (1,3) galactosyltransferase, the lack of guidance concerning xenogeneic cell selection and/or vector/gene selection such that the level of induced hyperacute immune responses in vivo correlates with tumor killing, the limitation of the working examples to the administration of murine vector producer cells which produce a retrovirus encoding HSV-TK and/or alpha (1,3) galactosyltransferase, and the breadth of the claims, it would have required undue experimentation to practice the scope of the invention as claimed and the skilled artisan would not have predicted success in treating tumors by inducing hyperacute immune responses using any means in the vicinity of the tumor.

The rejection of claims 6-8 and 15-16 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection of the claims for reasons of record as discussed in detail below.

The applicant argues that the amendments to claims 6 and 16 overcome the instant grounds of rejection and that the claims as written are clear and definite. Applicant's amendments to claims 6 and 16 have not introduced any particular step to the instant methods. The method claims as written fail to recite any particular step which results in the induction of hyperacute rejection or the treatment of tumors. "inducing a hyperacute rejection" and "inducing an

intraperitoneal inflammatory response" are not method steps. These limitations describe the effect of the missing step(s). In the absence of any particular recited method steps, these claims are indefinite as it is unclear what exactly are the metes and bounds of the invention.

Claim Rejections - 35 USC § 102

The rejection of claims 1, 3-4, 6, 9-12, and 15-16 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,045,789, hereafter referred to as Culver et al., is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that Culver et al. does not teach all the limitations of the instant invention and therefore cannot anticipate the claims. Specifically, the applicant argues that Culver et al. does not teach that the xenogeneic cells have a surface glycosylation pattern that includes alpha (1,3) galactosyl epitopes, or teach the use of HSVtk gene activation of GCV leading to a bystander killing of tumor cells. Claims 1, 6, 9-11, and 15-16 do not recite either of these limitations. Case law clearly teaches that claims are to be given their broadest reasonable interpretations, and that limitations taught in the specification which are not recited in the claims are not to be read into the claims. *In re Van Guens*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In regards to claims 3, 4 and 12, while Culver does not explicitly teach that the murine cells express alpha (1,3) galactosyl epitopes, it is an inherent property of murine cells that they

utilize alpha (1,3) galactosyltransferase in protein glycosylation and that murine proteins contain alpha (1,3) galactosyl epitopes. Alpha (1,3) galactosyl transferase is ubiquitously expressed in murine cells as part of the normal glycosylation machinery present in cells. Applicant's arguments regarding the lack of support in case law for inherency in process claims have been addressed above. See *Ex parte Novitski*. Further, in the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPAI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ2d 1922, 1923 (BPAI 1989).

The rejection of claims 1-4, 6-12, and 15 under 35 U.S.C. 102(a) over Klatzmann et al. is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that Klatzmann et al. does not teach all the limitations of the instant invention and therefore cannot anticipate the claims. Specifically, the applicant argues that Klatzmann et al. does not teach that the xenogeneic cells have a surface glycosylation pattern that includes alpha (1,3) galactosyl epitopes, or teach the use of a retrovirus to express both alpha (1,3) galactosyl transferase and HSVtk. Please note that claims 1-2, 6-11, and 15 do not recite either of these limitations. In regards to the induction of hyperacute rejection of tumors,

Klatzmann et al. clearly observed local inflammatory reactions at the tumor site following the injection of the xenogeneic cells and specifically states that the transplanted murine cells are rejected within 7-10 days as a result of hyperacute rejection mediated by preformed antixenogeneic antibodies and complement (Klatzmann et al., page 2585, abstract). Finally, applicant's arguments regarding the inherent expression of alpha (1,3) galactosyl epitopes by murine cells has been addressed in detail above.

The rejection of claims 1, 3-6, and 9-17 under 35 U.S.C. 103 over U.S. Patent No. 6,045,789, hereafter referred to as Culver et al. in view of Link et al., and further in view of Levy et al. is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

In response to applicant's arguments that the office has used hindsight reasoning, it is noted that "[a]ny judgement on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper." In re *McLaughlin,* 443 F2d. 1392, 170 USPQ 209, 212 (CCPA 1971). In response to applicant's specific argument that Culver doesn't teach the production of murine retroviral vectors with the addition of a gene encoding alpha (1,3) galactosyl transferase, it is noted that the test for

combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

The previous office action cited Culver for teaching the treatment of tumors comprising the administration of xenogeneic murine retrovirus producing cells directly to a tumor in a subject which includes humans wherein the murine cells produce a retrovirus which encodes HSV-TK and IL-2 such that an immune response is generated against the tumor and that tumor cells are killed directly by HSV-TK/ganciclovir or indirectly by innocent bystander effect. Culver et al. was also cited for teaching that many different types of retroviral vectors including replication-competent, replication-defective, amphotropic or xenotropic retroviral vectors are suitable for use in the disclosed methods. Link et al. was cited to supplement Culver et al. by teaching the LTKOSN.1 vector, a retroviral vector encoding HSV-TK, which can be produced by a murine retroviral producer cell line and which can be used for the killing of cells in combination with ganciclovir (Link et al., abstract). Thus, based on the teachings of Culver et al., that many different retroviral vectors encoding HSV-TK can be used to treat tumors using the disclosed methodology, and the successful expression of HSV-TK in cells using the LTKOSN.1 vector taught by Link et al., it would have been prima facie obvious to the skilled artisan at the time of filing to use the LTKOSN.1 vector taught by Link in the method of treating tumors taught by Culver et al., and the skilled artisan would have had a reasonable expectation of success in transducing tumor cells with the LTKOSN.1 vector.

The previous office acknowledged that neither Culver et al. nor Link et al. teaches the addition of the gene for alpha (1,3) galactosyltransferase to a retrovirus encoding HSV-TK. Culver, however, as discussed above, does teach the addition of genes which encode immune response-enhancing genes which activate a particular constituent of the immune system or which stimulates the proliferation of cells associated with an immune response (Culver et al., columns 8-9, lines 39-67 and 1-26). Levy et al. was cited to supplement Culver et al. and Link et al. by teaching methods of inducing hyperacute rejection of human tumor cells by contacting the tumor cells with murine retroviral producer cells which express alpha (1,3) galactosyltransferase (Levy et al., pages 2301-2302). Thus, in view of the motivation to include genes which encode immune response-enhancing genes which activate a particular constituent of the immune system in a retroviral vector encoding HSV-TK provided by Culver et al., and further in view of the successful generation of hyperacute immune responses against tumors exposed to retroviral producer cells expressing alpha (1,3) galactosyltransferase, it would have been prima facie obvious to the skilled artisan to modify the HSV-TK retroviral vectors taught by Culver et al. or Link et al. to further include the alpha (1,3) galactosyltransferase as taught by Levy et al. in order to increase hyperacute rejection of tumors and overall tumor treatment. Further, based on the successful killing of human tumor cells using both retrovirus encoded HSV-TK or alpha (1,3) galactosyltransferase, the skilled artisan would have had a reasonable expectation of success in treating tumors by combining the two therapeutic modalities in a single retroviral producer cell.

Finally, the applicant is reminded that for the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988). Note also that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988).

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be

reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé